

WHAT IS CLAIMED IS:

1. A method for achieving sustained therapeutic or prophylactic blood concentrations of a drug or active metabolite thereof in the systemic circulation of an animal which method comprises orally administering to said animal a compound of formula (I):

D-Y-T (I)

wherein D is a drug having therapeutic or prophylactic activity when delivered to the systemic circulation of said animal; T is a moiety selected to permit the compound of formula (I) or a active metabolite thereof to be translocated across the intestinal wall of an animal and participate in the enterohepatic circulation in said animal; and Y is a cleavable linker covalently connecting D to T wherein Y is selected such that a portion of the linker is cleaved to release drug D or active metabolite thereof during each cycle through the enterohepatic circulation whereupon sustained release of drug D in said animal is achieved.

2. A compound of formula (I):

D-Y-T (I)

wherein D is a drug having therapeutic or prophylactic activity when delivered to the systemic circulation of said animal; T is a moiety selected to permit the compound of formula (I) or a active metabolite thereof to be translocated across the intestinal wall of an animal and participate in the enterohepatic circulation in said animal; and Y is a cleavable linker covalently connecting D to T wherein Y is selected such that a portion of the linker is cleaved to release drug D or active metabolite

thereof during each cycle through the enterohepatic circulation whereupon sustained release of drug D in said animal is achieved.

3. A pharmaceutical composition comprising a pharmaceutically acceptable diluent and an effective amount of a compound of formula (I):



wherein D is a drug having therapeutic or prophylactic activity when delivered to the systemic circulation of said animal; T is a moiety selected to permit the compound of formula (I) or a active metabolite thereof to be translocated across the intestinal wall of an animal and participate in the enterohepatic circulation in said animal; and Y is a cleavable linker covalently connecting D to T wherein Y is selected such that a portion of the linker is cleaved to release drug D or active metabolite thereof during each cycle through the enterohepatic circulation whereupon sustained release of drug D in said animal is achieved.

4. A method for achieving sustained therapeutic or prophylactic blood concentrations of a drug or active metabolite thereof in the systemic circulation of an animal which method comprises orally administering to said animal a compound of formula (I):



wherein D is a drug having therapeutic or prophylactic activity when delivered to the systemic circulation of said animal; T is a moiety selected to permit the compound of formula (I) or a active metabolite thereof to be translocated across the intestinal wall of an animal and participate in the enterohepatic circulation in said animal; and Y is a

cleavable linker covalently connecting D to T wherein Y is selected to provide for sustained release of drug D in said animal for a period of at least about 10% longer than the oral delivery of drug D itself.

5

5. A compound of formula (I):



10

wherein D is a drug having therapeutic or prophylactic activity when delivered to the systemic circulation of said animal; T is a moiety selected to permit the compound of formula (I) or a active metabolite thereof to be translocated across the intestinal wall of an animal and participate in the enterohepatic circulation in said animal; and Y is a cleavable linker covalently connecting D to T wherein Y is selected to provide for sustained release of drug D in said animal for a period of at least about 10% longer (more preferably at least 50% longer and still more preferably at least 100% longer) than the oral delivery of drug D itself.

15

6. A pharmaceutical composition comprising a pharmaceutically acceptable diluent and an effective amount of a compound of claim 5.

20

25

7. A method of claim 1 wherein T is a selected to permit the compound of formula (I) or active metabolite thereof to be translocated across the intestinal wall of an animal via interaction with an intestinal transporter of the bile acid transport system or via passive diffusion, and to participate within the enterohepatic circulation.

30

8. The method of claim 7 wherein the intestinal transporter is selected from the group consisting of IBAT, an organic anion transporter polypeptide (OATP) or an organic anion transporter (OAT).

9. The method of claim 8 wherein the intestinal transporter is
IBAT.

5 10. A method of claim 7 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more hepatocyte anion transporters selected from group consisting of the bile acid transporters, organic anion transporter polypeptides (OATPs) or organic anion transporters (OATs), or via passive diffusion.

10 11. The method of claim 10 wherein the one or more hepatocyte transporters are selected from the group consisting of NTCP (or LBAT), OATP-A, OATP-B, OATP-C/LST-1, OATP-8, MPR2, BSEP or MDR3.

15 12. The method of claim 11 wherein the one or more hepatocyte transporters are selected from the group consisting of NTCP (or LBAT), MPR2 or BSEP.

20 13. A method of claim 1 wherein T is a selected to permit the compound of formula (I) or active metabolite thereof to be translocated across the intestinal wall of an animal via interaction with an intestinal anion transporter or via passive diffusion, and to participate within the enterohepatic circulation.

25 14. The method of claim 13 wherein the intestinal anion transporter is selected from the group consisting of the MCT's, OAT's, OATP's, SMVT, prostaglandin transporters, long chain fatty acid transporters, folate transporters and IBAT.

30 15. The method of claim 13 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more

hepatocyte anion transporters selected from group consisting of the bile acid transporters, organic anion transporter polypeptides (OATPs) or organic anion transporters (OATs), or via passive diffusion.

5 16. The method of claim 15 wherein the one or more hepatocyte transporters are selected from the group consisting of NTCP (or LBAT), OATP-A, OATP-B, OATP-C/LST-1, OATP-8, MPR2, BSEP or MDR3.

10 17. A method of claim 1 wherein T is a selected to permit the compound of formula (I) or active metabolite thereof to be translocated across the intestinal wall of an animal via interaction with an intestinal cation transporter or via passive diffusion, and to participate within the enterohepatic circulation.

15 18. The method of claim 17 wherein the intestinal cation transporter is selected from the group consisting of OCT1, OCTN1, OCTN2 and the polyamine transporters.

20 19. The method of claim 17 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more hepatocyte cation transporters selected from group consisting of the OCTs, MDR1 and related ABC binding cassette transporters, or via passive diffusion.

25 20. A method of claim 1 wherein T is a selected to permit the compound of formula (I) or active metabolite thereof to be translocated across the intestinal wall of an animal via interaction with an intestinal peptide transporter or via passive diffusion, and to participate within the enterohepatic circulation.

30 21. The method of claim 20 wherein the intestinal peptide transporter is selected from the group consisting of PEPT1 and PEPT2.

22. The method of claim 20 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more hepatocyte anion transporters selected from group consisting of the bile acid transporters, organic anion transporter polypeptides (OATPs) or organic anion transporters (OATs) or via passive diffusion.

23. The method of claim 22 wherein the one or more hepatocyte transporters are selected from the group consisting of NTCP (or LBAT), OATP-A, OATP-B, OATP-C/LST-1, OATP-8, MPR2, BSEP or MDR3.

24. The method of claim 20 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more hepatocyte cation transporters selected from group consisting of the OCTs, MDR1 and related ABC binding cassette transporters, or via passive diffusion.

25. The method of claim 4 wherein T is a selected to permit the compound of formula (I) or active metabolite thereof to be translocated across the intestinal wall of an animal via interaction with an intestinal transporter of the bile acid transport system or via passive diffusion, and to participate within the enterohepatic circulation.

26. The method of claim 25 wherein the intestinal transporter is selected from the group consisting of IBAT, an organic anion transporter polypeptide (OATP) or an organic anion transporter (OAT).

27. The method of claim 26 wherein the intestinal transporter is IBAT.

28. A method of claim 25 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular

membranes of hepatocytes in an animal via interaction with one or more hepatocyte anion transporters selected from group consisting of the bile acid transporters, organic anion transporter polypeptides (OATPs) or organic anion transporters (OATs), or via passive diffusion.

5

29. The method of claim 28 wherein the one or more hepatocyte transporters are selected from the group consisting of NTCP (or LBAT), OATP-A, OATP-B, OATP-C/LST-1, OATP-8, MPR2, BSEP or MDR3.

10

30. The method of claim 29 wherein the one or more hepatocyte transporters are selected from the group consisting of NTCP (or LBAT), MPR2 or BSEP.

15

31. A method of claim 4 wherein T is a selected to permit the compound of formula (I) or active metabolite thereof to be translocated across the intestinal wall of an animal via interaction with an intestinal anion transporter or via passive diffusion, and to participate within the enterohepatic circulation.

20

32. The method of claim 31 wherein the intestinal anion transporter is selected from the group consisting of the MCT's, OAT's, OATP's, SMVT, prostaglandin transporters, long chain fatty acid transporters, folate transporters and IBAT.

25

33. The method of claim 31 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more hepatocyte anion transporters selected from group consisting of the bile acid transporters, organic anion transporter polypeptides (OATPs) or organic anion transporters (OATs), or via passive diffusion.

30

RECEIVED
U.S. PATENT AND TRADEMARK OFFICE
JULY 10 2014

34. The method of claim 33 wherein the one or more hepatocyte transporters are selected from the group consisting of NTCP (or LBAT), OATP-A, OATP-B, OATP-C/LST-1, OATP-8, MPR2, BSEP or MDR3.

5 35. A method of claim 4 wherein T is a selected to permit the compound of formula (I) or active metabolite thereof to be translocated across the intestinal wall of an animal via interaction with an intestinal cation transporter or via passive diffusion, and to participate within the enterohepatic circulation.

10 36. The method of claim 35 wherein the intestinal cation transporter is selected from the group consisting of OCT1, OCTN1, OCTN2 and the polyamine transporters.

15 37. The method of claim 35 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more hepatocyte cation transporters selected from group consisting of the OCTs, MDR1 and related ABC binding cassette transporters, or via passive diffusion.

20 38. A method of claim 4 wherein T is a selected to permit the compound of formula (I) or active metabolite thereof to be translocated across the intestinal wall of an animal via interaction with an intestinal peptide transporter or via passive diffusion, and to participate within the enterohepatic circulation.

25 39. The method of claim 38 wherein the intestinal peptide transporter is selected from the group consisting of PEPT1 and PEPT2.

30 40. The method of claim 38 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more hepatocyte anion transporters selected from group consisting of the bile acid

transporters, organic anion transporter polypeptides (OATPs) or organic anion transporters (OATs) or via passive diffusion.

5 41. The method of claim 40 wherein the one or more hepatocyte transporters are selected from the group consisting of NTCP (or LBAT), OATP-

A, OATP-B, OATP-C/LST-1, OATP-8, MPR2, BSEP or MDR3.

10 42. The method of claim 38 wherein the compound of formula (I) or active metabolite thereof is translocated across the sinusoidal and canilicular membranes of hepatocytes in an animal via interaction with one or more hepatocyte cation transporters selected from group consisting of the OCTs, MDR1 and related ABC binding cassette transporters, or via passive diffusion.

RECEIVED
U.S. PATENT AND TRADEMARK OFFICE
JULY 10 2014